REMARKS

Status of the Claims

Claims 11-21 are currently pending in the application. Claims 11-13 stand rejected. Claims 11-13 have been amended as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. New claims 14-21 are presented herein. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 11 is supported by the specification at, for instance, page 8, lines 10-17. New claims 14-19 are supported generally by terms in claims 11-13 which have been deleted herein. New claims 20 and 21 are supported by the specification at, for instance, Examples 1-4. Reconsideration is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 11-13 stand rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See*, Office Action of June 13, 2007, at page 2, hereinafter, "Office Action"). Applicants traverse the rejection as set forth herein.

The Examiner states that type A and type B solvents are unclear and/or indefinite. Furthermore, the Examiner states that the claims are indefinite because they recite the term "preferably." According to the Examiner, it is uncertain whether the phrases beginning with "preferably" are intended to be positive limitations or not.

Although Applicants do not agree that claims 11-13 are indefinite, to expedite prosecution, claim 11 has been amended herein without prejudice or disclaimer to be directed to

a first and a second solvent, "wherein the first solvent is selected from at least one of the group consisting of: an aprotic solvent that is less polar than the second solvent and a dipolar aprotic solvent, and wherein the second solvent is selected from at least one of the group consisting of: an aprotic solvent, a dipolar aprotic solvent and an apolar solvent." Support for this amendment may be found throughout the specification at, for instance, page 8, lines 10-17.

Claims 12 and 13 have been similarly amended and the term "preferably" removed therefrom without prejudice or disclaimer. The subject matter following the terms "preferably" removed from these claims has been presented in new dependent claims 14-19.

Reconsideration and withdrawal of the indefiniteness rejection of claims 11-13 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 11-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over in view of Lifshitz-Liron et al., WO 03/051362 (hereinafter, "Lifshitz-Liron et al."). (*See*, Office Action, at pages 2-4). Applicants traverse the rejection as hereinafter set forth.

The Examiner states that the presently claimed invention differs from that of Lifshitz-Liron et al. because Lifshitz-Liron et al. do not disclose or suggest the addition of sulfuric acid to clopidogrel free base dissolved in a solvent, or adding sulfuric acid mixed with a solvent to the solution of clopidogrel free base. However, the Examiner states that the use of different solvents to optimize the presently claimed process is routine to one of ordinary skill in the art. Therefore, the Examiner concludes that the presently claimed process would be obvious to one of ordinary skill in the art.

Applicants believe the Examiner has failed to properly consider the required factors of an obviousness rejection. *Graham v. John Deere*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966) has provided the controlling framework for an obviousness analysis. A proper analysis under 35 U.S.C. § 103(a) requires consideration of the four *Graham* factors of: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims that are at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). (*See*, *Graham v. John Deere*, 383 U.S. at 17, 148 U.S.P.Q. at 467).

More specifically, Applicants believe that the Examiner has not properly or sufficiently considered factors 1 and 2 because Applicants do not agree with the Examiner's analysis of the disclosure of Lifshitz-Liron et al. and its differences from the presently claimed methods, at least as reflected in amended claims 11-13. Applicants believe the Examiner is improperly interpreting the disclosure of Lifshitz-Liron et al. and the knowledge of one of ordinary skill in the art.

Lifshitz-Liron et al. describe two different methods for the preparation of an amorphous form of clopidogrel hydrogensulphate, summarized as follows:

1) Preparation of clopidogrel hydrogensulphate salt by an "*in situ*" reaction of sulphuric acid with clopidogrel base in acetone (Examples 16 and 17). The amorphous product was evaporated to dryness. The treatment of these reaction mixtures, namely the evaporation to dryness under reduced pressure and the subsequent discharge, is very disadvantageous when performed on an industrial scale. Furthermore, the use of a solvent to help the discharge of the

reaction equipment may cause an undesirable crystallization of the product. This process is very different from the technical solution of the presently claimed invention.

2) The second method involves a dissolution-precipitation process, in which clopidogrel hydrogensulphate is dissolved in an alcohol type solvent, then precipitated with a so-called "antisolvent."

The advantage of the use of alcohols in the Lifshitz-Liron et al. process is the fact that clopidogrel hydrogensulphate is very soluble in protic solvents. Adding this solution to a large amount of the "antisolvent" or adding the "antisolvent" to the clopidogrel solution results in an extreme change of the polarity of the reaction mixture, which precipitates the salt in an amorphous form. (*See*, Examples 13, 14 and 15 of Lifshitz-Liron et al.).

Thus, the volume of the antisolvents required in the method of Lifshitz-Liron et al. is about 150-460 times higher than the weight of the clopidogrel base content of the resulting reaction mixture.

However, the prior art methods have many significant drawbacks, summarized as follows.

A) Formation of an alkyl hydrogensulphate compound, which is a very harmful alkylating agent. (*See*, "A Modern Approach to Organic Chemisty," at pages 175-176, a copy of which is attached hereto as Exhibit A). This process takes place in mild conditions too, as it is shown in the enclosed Example. (*See*, additional Experimental Data, attached hereto as Exhibit B).

Lifshitz-Liron et al. do not disclose the purity of the products obtained from their methods. The detection and elimination of these by-products is not easy. The steps for the elimination of this process can modify the polymorph form of the product.

B) Transesterification of the clopidogrel base itself using an alcohol different from methanol. (*See*, "A Modern Approach to Organic Chemisty," at pages 282-283, a copy of which is attached hereto as Exhibit C).

Based on the facts described above, there are definite technological and chemical drawbacks of the processes suggested for the preparation of an amorphous form of clopidogrel hydrogensulphate according to the disclosure of Lifshitz-Liron et al. Thus, Lifshitz-Liron et al. clearly teach away from the presently claimed methods. In fact, these disadvantages make the use of these processes on an industrial scale almost impossible.

Distinguishing Features and Advantages of the Presently Claimed Methods

According to the present invention two technical parameters are changed simultaneously (first solvent and the "*in situ*" preparation of the salt) as compared to the method of Lifshitz-Liron et al. in order to achieve the successful preparation of a pure amorphous form of clopidogrel hydrogensulphate in a reproducible process which is suitable for industrial scale. These features are described hereinbelow in more detail.

A. Polar aprotic solvents are used as the first solvent instead of alcohols.

Example 12 is the only example in which Lifshitz-Liron et al. apply the dissolution-precipitation process using a solvent other than alcohol. Similar to Example 15 of Lifshitz-Liron et al., in which methanol is used as the first solvent, the volume of the antisolvent is 460 times as much as the weight of the clopidogrel base content of the resulting reaction mixture: 0.71g (71% yield) clopidogel hydrogensulphate is obtained from a mixture of 350 ml of diethyl ether and 6 ml of acetonitrile.

These results clearly show that the use of a dipolar aprotic solvent as the first solvent results in a polymorph form II even when using a large amount of the second solvent for precipitation. These results would dissuade a person of ordinary skill in the art from changing the solvent, and thus teach away from the presently claimed methods.

B) Choice of the "*in situ*" preparation of the salt in the first solvent.

Several examples in Lifshitz-Liron et al., such as Examples 1-11, 31-37, 41, disclose reactions of clopidogrel base and sulphuric acid in different solvents. In most of these cases the inventors did not use the dissolution-precipitation process, thus different crystalline polymorph forms were obtained.

In Examples 16 and 17 of Lifshitz-Liron et al., in which the "*in situ*" preparation of the salt results in an amorphous form, acetone was used as solvent. As mentioned above, in this case the salt had to be evaporated to dryness in order to obtain the amorphous product.

These facts also teach away from the presently claimed methods because they do not encourage one of ordinary skill in the art to prepare the salt "*in situ*" in the first solvent.

Further, as to new claims 20 and 21, as a result of the reduction of the amount of the second solvent in Examples 39 and 41 of Lifshitz-Liron et al., crystalline polymorph forms were obtained. The only possible reason for this change is that the polarity of the reaction mixture did not change enough to prevent the crystallisation of the active ingredient. These examples therefore also teach away from the presently claimed methods, as recited in at least new claims 20 and 21, because they dissuade one of ordinary skill in the art to reduce the use of the amount of the apolar second solvent.

Any cited reference used for a rejection under 35 U.S.C. § 103(a) must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from a claimed invention. (*See*, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). In other words, Lifshitz-Liron et al. must be read in its entirety, including the parts of the disclosure which clearly teach away from the presently claimed methods, for instance in that using a dipolar aprotic solvent as the first solvent would have disadvantages.

Further, a reference which leads one of ordinary skill in the art away from the claimed invention cannot render it unpatentably obvious. (*See*, *Dow Chem. Co. v. American Cyanamid Co.* 816 F2d 617, (CAFC 1987)).

In this regard, a claimed combination cannot change the principle of operation of the primary reference or render a reference inoperable for its intended purpose. (*See*, M.P.E.P. §§ 2143.01, sections entitled "The Proposed Modification Cannot Render the Prior Art Unsatisfactory For Its Intended Purpose" and "The Proposed Modification Cannot Change the Principle of Operation of a Reference," and M.P.E.P. § 2145(III)). The Federal Circuit has also

held: "If references taken in combination would produce a 'seemingly inoperative device,' we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness." (*See*, *McGinley v. Franklin Sports Inc.*, 60 U.S.P.Q.2d 1001, 1010 (CAFC 2001), citing *In re Sponnoble*, 405 F.2d 578, 587, 160 U.S.P.Q. 237, 244 (CCPA 1969), holding that references teach away from combination if combination produces seemingly inoperative device; and *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984), finding that an inoperable modification teaches away).

Objective Evidence of Unexpected Results

Applicants surprisingly found that the change of the protic solvent to a dipolar aprotic solvent and the use of an "*in situ*" process for the preparation of the salt according to the presently claimed methods results in a new process which unexpectedly does not have the drawbacks of the processes according to Lifshitz-Liron et al.

The advantages of the process according to the present invention are summarized in the following tables:

Lifshitz-Liron et al.

Examples	Solvent	Antisolvent	Yield%	Notes
13	Methanol	Toluene	42 %	
14	Methanol	Diethyl ether	56%	
15	Methanol	Diethyl ether	86%	
12 *	Acetonitrile	Diethyl ether	71%	Polymorph II

Present Invention

Examples	Solvent	Antisolvent	Yield%	Notes
1	Acetone	Diisopropyl ether	90,5%	
2	Dichloromethane	Diisopropyl ether	88,1%	
3	Dichloromethane	Cyclohexane	92,8%	
4	Dichloromethane	Ethyl acetate	82%	

Therefore, Applicants believe the Examiner has failed to establish a *prima facie* case of obviousness with respect to the presently claimed invention. Specifically, the Examiner has not properly taken into account all four factors of the *Graham* factor analysis, including those sections of the cited references that teach away from the presently claimed invention.

Additionally, even if, *arguendo*, the Examiner believes a *prima facie* case of obviousness has been made, Applicants' Examples 1-4 disclosed in the specification and the test results attached hereto certainly provide sufficient objective evidence of unexpected results to warrant a finding of non-obviousness.

Reconsideration and withdrawal of the obviousness rejection of claims 11-13 are respectfully requested.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

Marc S. Weiner
Registration No.: 32,181
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicants

Attachments: Appendix A - "A Modern Approach to Organic Chemisty," at pages 175-176
Appendix B - Experimental Data, 8 pages
Appendix C - "A Modern Approach to Organic Chemisty," at pages 282-283